IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/564,372	Confirmation No. 9406
Applicants	:	Frank SCHILKE et al.	
Filed	:	July 16, 2004	
Title	:	USE OF ANTISEPTIC ACTIVE PRINCIPLES IN PMMA BONE CEMENTS	
Group Art Unit	:	1613	
Examiner	:	Blessing M. Fubara	
Customer No.	:	28289	

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DECLARATION UNDER 37 C.F.R. § 1.132

I, **Frank Schilke,** hereby declare as follows:

1. I am a co-inventor of the invention disclosed and claimed in the subject patent application, U.S. Patent Application Serial No. 11/564,372.

2. Since receiving a degree in Chemistry (degree as Diplomchemiker, equivalent to Master of Science) at the Martin-Luther-University Halle where I studied from 1991 to 1996, I have been working in the field of PMMA bone cement research for many years. Since 2001, I have been an employee of Biomet Deutschland GmbH (the assignee of the present application) and have been responsible since 2006 for quality control of PMMA bone cement products for Biomet Switzerland GmbH (which is a related company).

3. I have reviewed the above-identified patent application, the pending

claims thereof, the Office Action of August 23, 2010 and cited references, including the rejection of claims 7-16 under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,980,573 ("Shaffner") in view of U.S. Patent No. 5,019,096 ("Fox, Jr. et al.") and further in view of U.S. Patent No. 5,997,544 ("Nies et al.") and U.S. Patent No 5,942,218 ("Kirschner et al.") as set forth in the Office Action for the above-identified patent application. I have reviewed and considered the cited prior art as set forth in the Office Action, and I believe that none of the cited prior art, combined as set forth in the Office Action, discloses or suggests the method of preventing microbial colonization of a bone cement surface of claim 7.

4. I am familiar with the disclosure of Shaffner (U.S. Patent No. 5,980,573). Shaffner relates to a prosthetic device for placement in an implant area of the body (Abstract). This device can be used for replacement of implanted device in order to fight and prevent infections. Accordingly, the prosthesis comprises a material such as PMMA bone cement which is impregnated with an antibiotic (column 3, lines 54-55). Shaffner does not suggest or disclose use of a non-antibiotic **antiseptic** compound such as polyhexamethylene biguanide ("PHMB").

5. Antibiotics, however, are known for causing resistance if used over a long time period. In contrast, antiseptics, such as PHMB, are not known to promote an increase in resistant germs. This is due to the different modes of actions of antibiotics and antiseptics. Antibiotics have a selective toxicity against specific bacteria, while antiseptics usually inhibit, but do not always kill, the growth of microorganisms.

It was an object of the present invention to replace the antibiotic in conventional bone cements with a novel medicament to prevent microbial colonization on the surface of the cement (Specification at page 2, lines 7-17). This object was solved by using PHMB. Surprisingly, PHMB was not only able to diffuse out of the bone cement, but also showed an improved antimicrobial effect.

This improved effect is shown in the diagrams of Figs. 1a and 1b, which clearly show that the use of PHMB provided an improved effect compared to the conventionally applied antibiotic gentamicin. When **0.155 %** PHMB was used, almost no colonization of the cement

surface with Staphylococci was detectable even after 7 days of incubation. In contrast, when using the much larger amount of **0.86 %** gentamicin, the cement surface was strongly colonized with Staphylococci. Thus, PHMB exhibited an improved antimicrobial effect compared to gentamicin.

In my opinion, this result was surprising and thus not predictable by a person skilled in the art.

6. I am familiar with the disclosure of Fox Jr., et al. (U.S. Patent No. 5,019,096). This patent relates to a method of preparing an infection resistant medical device, wherein the device comprises a coating containing an antimicrobial compound (Abstract). Preferred coating materials are polyurethane, silicon or degradable polymers (col. 2, lines 12-16). A combination of a silver salt and a biguanide, in particular chlorhexidine, is used as an antimicrobial compound (column 2, lines 10 to 27).

However, chlorhexidine does not have a very good biocompatibility. The compound chlorhexidine described in **Fox et al.** is a low molecular biguanide derivative with a molecular weight of 505. It is known to use small compounds with good water solubility for obtaining an antiseptic effect on the cement surface or in the surrounding thereof, in particular due to their good diffusion properties.

In contrast, higher molecular weight compounds are usually characterized by a low diffusion rate. In such case, it had only been possible so far to increase the diffusion rate by increasing the concentration in the bone cement or to increase the permeability of the cement matrix by adding further additives or auxiliaries to the cement.

Therefore, it was completely unexpected that, by combining PMMA cement and polyhexamethylene biguanide (PHMB), the higher molecular weight PHMB was able to diffuse from the bone cement and provide long-lasting prevention of microbial colonization of the PMMA surface.

Furthermore, it was surprisingly found that very low amounts of the higher molecular weight PHMB suppressed colonization of the cement surface of the bone cement by pathogenic bacteria in an effective manner. This is even more surprising, since PHMB has

inferior prerequisites for release from PMMA bone cement compared to the usually applied gentamicin (see Figs. 1A and 1B in the application). Due to the high molecular weight of PHMB of more than 1700, it was not expected that this substance with a low concentration of up to 1 weight% to the PMMA bone cement would be released in an effective amount during the relatively long time range of more than 7 days.

The data of Figs. 1A and 1B clearly show the diffusion of PHMB from the bone cement. If this wasn't true, no antimicrobial effect on the tested Staphylococci would be detectable. If no PHMB diffusion occurred, the number of determined germs would be the same for both plain bone cement (Palamed plain) and the PHMB containing bone cement. However, this is not the case as shown in the diagrams of Fig. 1A and 1B. Therefore, a person skilled in the art would understand that the data in Figs. 1A and 1B show diffusion of PHMB from the bone cement.

In the present invention, it has been described for the first time that the simple combination of high molecular PHMB and PMMA bone cement shows an effective antiseptic effect without any further measures. Upon information and belief, I believe that the antiseptic effect of PHMB is not exclusively based on the simple release of the compound into the surrounding media and the destruction of the suspended germs, but is based upon unexpected synergy.

In fact, the surprisingly high and long-lasting effectiveness suggests an attachment or colonization of the polymeric cement surface by the released compound so that the compound is enriched on the surface in form of the thin layer. Similar observations were made in case of adhesion of polyethylene glycol (PEG) on polymeric surfaces whereby in this circumstance the similarity of PEG and PHMB in respect to some physical chemical properties has to be pointed out. Such a layer formation accounts for the unexpected effect that after incubation in a bacterial culture the colonization of the cement surface is effectively suppressed over a longer time period.

Therefore, in my opinion, it was not obvious for a person skilled in the art at the time of the present invention to conclude from the application of a smaller molecule such as chlorhexidine to use a compound having a high molecular weight, such as PHMB, to achieve the

unexpected high antiseptic effectiveness provided when mixing such a low amount of PHMB with PMMA bone cement. Rather, it contradicts the prevailing opinion that small, water soluble molecules are preferred for the release of compounds from solid polymeric carrier materials by matrix diffusion.

7. I am also familiar with the teaching of Nies et al. (U.S. Patent No. 5,997,544). Nies et al. describes a process and a device for producing sterile-packed bone cement to which amongst others antibiotics can be added (column 6, lines 34 to 38).

Thus, this document discloses solely the use of antibiotics and not antiseptics like PHMB.

8. Kirschner et al. (U.S. Patent No. 5,942,218) relates also to an anti-infective material for treatment and/or prophylaxis of wound infections which can comprise amongst others PHMB with a mean molecular weight of 2,900 to 15,000 (col. 2, lines 52-57). This substance can be used in form of aqueous solutions, emulsions, suspensions, gels and the like for wound treatment (col. 4, lines 6 to 16).

Kirschner et al. does not suggest or disclose the application of PHMB in bone cement. Therefore, one of ordinary skill in the art does not get any hint from this document that PHMB would diffuse from bone cement.

9. Based on the foregoing, it would not have been obvious for a person of ordinary skill in the art at the time of the present invention to apply the chlorhexidine described by **Fox et al.** in bone cement according to **Shaffner** or **Nies et al.** *with the aim of preventing the microbial colonization of the cement surface.*

Also, the application of the high molecular polyhexamethylene biguanide described by **Kirschner et al.** in bone cement was not obvious since it was surprising for a person skilled in the art that polyhexamethylene biguanide was released from bone cement at all. This effect is not disclosed or obvious in view of **Kirschner et al.**

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

15. NOV. 2010

Date

Mr. Frank Schilke